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Clinical report

Severe acute fatty liver in pregnancy: a diagnostic dilemma in clinical practice

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Background: Acute fatty liver of pregnancy (AFLP) is an uncommon complication in the third trimester of pregnancy. Differential diagnosis between severe cases of AFLP and others conditions remains challenging since there is no specific diagnostic test for this condition and the diagnosis is made by clinical and laboratory findings.
Objective: To evaluate the clinical presentation, laboratory findings, and clinical outcome in patients with acute fatty liver of pregnancy.
Material and Method: A retrospective study was carried out in all hospitalized pregnant patients who presented with hepatitis in the third trimester at King Chulalongkorn Memorial Hospital (KCMH), between January 2001 and March 2011. The diagnosis of AFLP had been made by clinical symptoms, laboratory evidence of acute hepatitis in the third trimester of pregnancy and by exclusion of other causes.
Results: Of 102,989 deliveries, there was five AFLP, giving an incidence of 1 in 20,598 pregnancies. The mean maternal age and gestational age was 33.6 years and 36 weeks, respectively. The mean length of stay in hospital was 12 days (range 8 to 20 days). Nausea and jaundice were the most common symptoms. It is of interest that one case of AFLP coexisted with the syndrome, which is a combined medical feature of "H" for hemolysis, "EL" for elevated liver enzymes, and "LP" for low platelet count (HELLP). Hypoglycemia was found in all patients requiring continuous infusion of dextrose solution. Acute renal failure was also found in all cases. Initial serum creatinine varied from 1.5 to 3.7 mg/dL. None of the patients required hemodialysis and renal function returned to normal at discharge. Two cases were associated with DIC, which caused postpartum hemorrhage. Liver function tests became normal within 7 to 43 days. There was one case of perinatal death of the fetus and no maternal deaths.
Conclusion: AFLP is an emergency. Multiple organ failures could develop even after delivery. In our experience, some cases of AFLP could overlap with HELLP syndrome or masquerade as TTP in the setting of pregnancy. Careful analysis of the clinical progression is important in the recognition of AFLP and prompt termination of the pregnancy is required to improve maternal and perinatal outcomes.

Keywords: Acute fatty liver of pregnancy, acute renal failure, disseminated intravascular coagulopathy

Acute fatty liver of pregnancy (AFLP) is a rare life-threatening obstetric emergency, which usually occurs during the third trimester with a reported maternal mortality varying from 5 to 26% [1]. Classically, AFLP was suspected in pregnant patients who presented with painless jaundice and modestly elevated transaminase occurring after the 35th week of pregnancy. The diagnosis of severe AFLP, which may be complicated by disseminated intravascular coagulation (DIC), renal failure, alteration of consciousness, is difficult due to overlapping of similar features with other conditions such as hemolytic anemia; elevated liver enzymes; low platelet count syndrome (HELLP), thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome (HUS) [2]. This challenging differential diagnosis is essential specific treatment, as plasmapheresis should be initiated early in cases of TTP.

Until the late 1970s AFLP had a dismal prognosis, with fetal and maternal mortality rates as high as 85% due to delay in diagnosis and lack of adequate supportive care [3]. In a more recent series [4], improved outcome with a maternal mortality rate of at about 5% was achieved because prompt delivery was undertaken along with improved medical

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treatment for fulminant hepatic failure. Given the rarity of AFLP, a retrospective review in our institute was conducted to analyze our own experience with this uncommon disease. We also present a challenging case of severe AFLP in detail to narrate the difficulty of arriving at an accurate diagnosis.

Material and method

A retrospective review of all patients who were hospitalized at King Chulalongkorn Memorial Hospital (KCMH), Bangkok, Thailand with hepatitis in the third trimester was conducted between January 2001 and March 2011. The diagnostic of AFLP was assessed by 'Swansea criteria', proposed by Ch'ng et al [5], which required more than six abnormal clinical symptoms and laboratory evidence of acute hepatitis in the third trimester of pregnancy without other possible diagnosis. Medical records of patients with a discharge diagnosis of AFLP were reviewed. The institutional review board approved the present study.

Statistical analysis

All statistical analyses were performed using SPSS (version 15.0; SPSS, Chicago, IL, U.S.A.). Means (±standard deviation, SD), median, and frequency (%) were used to describe demographic data.

Results

During the 11-year-period between January 2001 and March 2011, of 102,989 deliveries in our institute, five were clinically diagnosed with AFLP, giving an incidence of 1 in 20,598 pregnancies (**Table 1**). The clinical and laboratory features of AFLP in our series are summarized in **Table 2**. The mean maternal age and gestational age of our patients was 33.6 years and 36 weeks, respectively. The mean length of stay was 12 days (range 8 to 20 days). Nausea and jaundice were the most common symptoms. One case of AFLP also had HELLP (case3). Hypoglycemia was found in all patients requiring continuous infusion of dextrose solution. Acute renal failure was found in all cases. Initial serum creatinine varied from 1.5 mg/dL to 3.7 mg/dL. No patient required hemodialysis and renal function returned to normal at discharge. Two cases were associated with DIC, which caused postpartum hemorrhage. Three patients improved within one week postpartum except case 3 and the presented case that was critically ill at the time of presentation. Liver function tests turned to normal within seven to 43 days. One case of perinatal fetal death was from fetal distress, however, no maternal death was found in our experience.

Table 1. Maternal characteristics and complications in patients with acute fatty liver of pregnancy

Case	Age (yr)	Gravid	GA (wk)	Presenting symptom	Complication	Time to clinical improvement (days)	Time to LFT improvement (days)
1	38	G1P0	36	Jaundice	ARF, hypoglycemia	5	7
2	26	G1P0	36	Jaundice	ARF, hypoglycemia	6	10
3	33	G3P1A1	37	Jaundice	ARF, DIC, hypoglycemia	9	15
4	35	G2P1	35	Decreased fetal movement	ARF, hypoglycemia, perinatal death	6	16
5*	36	G3P1A1	38	Jaundice	ARF, DIC, hypoglycemia	13	43

*Presented case. Mean duration of time to clinical improvement = 7.8 days. Mean duration of time to LFT improvement = 18.2 days

Table 2. Laboratory findings at admission in patients with acute fatty liver of pregnancy

Case	TB (mg/dL)	DB (mg/dL)	AST/ALT (U/L)	ALP (U/L)	INR
1	11.6	11.0	247 / 226	354	1.4
2	10.1	5.9	74 / 104	508	1.3
3	11.2	10.5	196 / 258	540	2.1
4	8.4	7.7	684 / 503	467	1.7
5*	20.6	14.9	332 / 470	697	2.4

TB = Total bilirubin, DB = Direct bilirubin, Presented case. Range of total bilirubin (mean) = 8.36-20.6 mg/dL (12.37), range of ALT (mean) = 104-503 U/L (312.2), range of INR (mean) = 1.3-2.4 (1.78)

A challenging case in diagnosis of severe AFLP, who had progressive deterioration after delivery, was presented in detail.

Case report

A 36-year-old woman (gravida 3, para 1, abort 1) at 38 weeks of gestation presented with a 3-day history of jaundice and absence of fetal movements for 2 days. One month prior of this admission, she had a history of upper respiratory tract symptoms, which resolved within one week. After that, she complained of weakness, somnolence, and nausea for two weeks. She denied symptoms of abdominal pain, fever, or vomiting. She had lost four kilograms within two weeks. The patient had no significant past medical history except a previous spontaneous abortion in the first trimester 10 years ago. She took no other medications, did not take herbal supplements, and had no known allergies to medications. She also denied history of recent travel outside Bangkok.

On admission, vital signs were normal. Physical examination was remarkable for icteric sclera and slow fetal heart rate at 100 beats/ min. Others findings including neurologic examination were within normal limits. Initial laboratory results were as follows, hemoglobin 12.2 g/dL (13.5-16.5 g/dL), leukocytes 13,900 cell/mm^3 with a normal differential, platelets 155,000 cell/mm^3, international normalized ratio (INR) 2.4, and partial thromboplastin time (PTT) 27 seconds (control at 27 seconds). Blood chemistries revealed BUN 34 mg/dL, creatinine 3.7 mg/dL, SGOT 332 U/L (5-34 U/L), SGPT 470 U/L (5-34 U/L), alkaline phosphatase 697 U/L (40-150 U/L), total bilirubin 20 mg/dL, and directed bilirubin 14 mg/dL. Emergency cesarean section was performed immediately because of fetal distress. A 2,780 grams male newborn was delivered with birth asphyxia and respiratory distress, Apgar score was 1 at the first minute and 4 at the fifth minute. He was resuscitated in the operative room and transferred to neonatal intensive care unit (ICU).

The patient was found to be drowsy five hours after delivery from hypoglycemia (blood sugar 55 mg/dL). She was transferred to ICU and intravenous dextrose was given to maintain her blood sugar. Impending fulminate hepatic failure was initially suspected to account for her conditions. Acute fatty liver of pregnancy was also suspected from the initial presentation, however, progressive clinical deterioration after delivery made the diagnosis of AFLP doubtful at first. Viral hepatitis panels including hepatitis A, B, C, E, and serum ceruloplasmin were performed and were all within normal limit. Ultrasonography of hepato-biliary system showed slightly increased echogenicity of liver parenchyma. Over the next 24 hours, she still had relatively low blood sugar levels and worsening drowsiness. Neurological examinations revealed disorientation and flapping tremors. No immediate post-partum hemorrhage occurred. Follow-up laboratory tests demonstrated rapid decreased of hemoglobin from 12.2 g/dL to 8.3 g/dL, deteriorating platelet counts of 103,000 cell/mm^3, and slightly worsening of INR at 2.5. The peripheral blood smear showed the presence of microangiopathic microcytic anemia (MAHA). Urinalysis revealed trace proteinuria with red blood cell 5-10 cell per field. Serum lactate dehydrogenase (LDH) level was elevated at 858 U/L (normal upper limit, 480 U/L) and serum uric acid was slightly elevated at 7.8 mg/dL (normal range, 3-5.5 mg/dL).

Computed tomography of brain revealed generalized brain edema without bleeding. At this point, HELLP was also suspected. However, the patient's condition of both HELLP and AFLP usually improve after delivery. Therefore, TTP, which can be a primary condition or develop as a co-existing condition with an initial illness, was also in our differential diagnosis. The laboratory tests for DIC panels and von Willebrand factor-cleaving protease ADAMTS13 were sent to find out the cause of MAHA. Plasmapheresis with fresh frozen plasma was initiated because her clinical conditions deteriorated rapidly.

At the fourth day of admission, the patient developed hemoperitoneum and hypovolemic shock due to worsening of coagulopathy. Emergency laparotomy was done finding unclotted blood 2,000 mL and blood oozing from muscle. Plasmapheresis was continued for three days, waiting for pending results for DIC panels and ADAMTS13 level that is a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, and its low level will support the diagnosis of TTP. After aggressive treatment in ICU, her clinical condition gradually improved as well. Liver and renal function tests are shown in **Table 1**. The DIC panel tests revealed slightly decreased fibrinogen level at 1.3 g/L (1.7-4.0 g/L) and prolonged euglobulin lysis time. These results suggested a diagnosis of DIC as the cause of MAHA rather than TTP and the ADAMTS13 level came back later with a normal level (72 U/dL).

Therefore, plasmapheresis was discontinued and supportive treatment was continued. The patient received supportive treatment with gradual recovery of hepatic and renal function and resolution of DIC at the 15th day after admission. Her child gradually recovered after supportive treatment in the neonatal intensive care unit and was discharged without any complication. The patient returned to a normal clinical condition and was discharged after three weeks of hospitalization. On follow-up visit at one month, the liver enzymes were normal and she appeared well.

Discussion

Liver diseases during pregnancy include intrahepatic cholestasis, preeclampsia, the HELLP syndrome, and acute fatty liver of pregnancy [6]. Many of these disorders are so uncommon that practicing clinicians might rarely encounter one during a career. Therefore, the accurate diagnosis might be missed, which could cause significant maternal and perinatal morbidity and mortality. AFLP is a rare obstetric emergency, which usually occurs after the 35 week of pregnancy. Differentiating AFLP from other causes of liver disease during pregnancy can be challenging because AFLP shares common features with other conditions and this disorder occurs with varying intensity [2, 7, 8]. However, if unrecognized or untreated, AFLP may progress to fulminant hepatic failure with jaundice, encephalopathy, disseminated intravascular coagulation, uncontrollable gastrointestinal and uterine bleeding, and death.

In a prospective, population-based study from the United Kingdom, it reported an estimated incidence of AFLP of one case per 20,000 births, which is similar to our experience [9]. The diagnosis of AFLP is always based on a clinical rather than histological diagnosis because of the presence of coagulopathy precluding liver biopsy. Moreover, there is no specific test to identify this condition even though liver biopsy will likely to demonstrate microvesicular fatty steatosis in the hepatocytes with minimal hepatocellular necrosis [7]. Histologic diagnosis is rarely required to aid in diagnosis. Typical cases of AFLP will have modestly elevated transaminase, generally less than 500 U/dL with elevation of bilirubin in the range of 5 to 10 mg/dL. However, in severe cases, the level of bilirubin could increase up to more than 40 mg/dL [10]. In our present study, the clinical and laboratory features of AFLP are consistent with other series [3-5, 7-11], including the hypoglycemia, which was found in all our patients.

Although most cases of AFLP resolve quickly after delivery, progressive disease leading to multi-organ failure, could develop as showed in our case [12]. Therefore, severe cases of AFLP could make more difficulty in differential diagnosis with other mimic conditions such as HELLP syndrome, HUS, or TTP. HELLP syndrome may present without the clinical signs of preeclampsia (hypertension and proteinuria or edema) in as many as 15 to 20% of affected patients [13]. It could develop as an overlapping syndrome in up to 50% of AFLP patients in some series [8-12]. Therefore, these two conditions may represent part of a spectrum of the same disease, which involves endothelial cell injury, platelet activation, and vasospasm [8]. The histological diagnosis could distinguish between HELLP syndrome where necrosis is predominantly in periportal areas [6]. The benefit in differentiating AFLP from HELLP is that the risk of recurrence in subsequent pregnancy is much higher in AFLP than HELLP. According to the study of Vigil-De Gracia P [8], hypoglycemia, elevated bilirubin levels, and prodromal vomiting were useful distinguishing features of AFLP in comparison with HELLP. In our case, the patient developed profound impending fulminant liver failure with DIC and hypoglycemia supported the diagnosis of AFLP.

As demonstrated in our case, another mimicking condition, which needs specific treatment, is thrombotic thrombocytopenic purpura with the constellation of typical symptoms (thrombocytopenia, MAHA, impaired renal function, neurologic symptoms, and fever). However, it may present with incomplete symptoms [14]. It is important to make an accurate diagnosis and begin plasmapheresis promptly because TTP is progressive and may be fatal if left untreated. Some studies tried to distinguish between TTP and HUS, but the presenting features are usually the same in adults, beginning with thrombocytopenia and MAHA. Therefore, many patients who have neurological abnormalities with acute renal failure represent a syndrome of TTP-HUS with variable clinical expression in a same disease process [15]. In clinical practice, it would be difficult to determine whether the presence of MAHA came from the DIC process in AFLP or TTP because multi-organ ischemia caused by thrombotic microangiopathy could predispose to DIC as well and TTP tends to develop in the setting of pregnancy [16]. Even though the von

Willebrand factor (vWF)–cleaving protease ADAMTS13 is a helpful marker for the diagnosis of sporadic classic immune-mediated TTP, if the level is very low to absent, this test is often not available to influence acute deci-sion-making regarding institution of treatment. As a result, plasmapheresis was initiated in our case due to the severity in our patient. With the recent advances in molecular genetics, some cases of AFLP were found to relate with a maternal/fetal genetic defect in the metabolism of free fatty acids (deficiency of long-chain 3-hydroxy acyl-coenzyme A dehydrogenase, LCHAD) [17, 18]. Several studies from Caucasian populations advocated the role of screening newborn at birth in pregnancies complicated by AFLP for this genetic disorder. However, recent reports from Japan and China failed to identify LCHAD mutation in patients with AFLP [19, 20]. Due to the sophisticated test for LCHAD mutation and difficulty in identify common mutations as previously described in Caucasian populations, the diagnosis of AFLP in our institute is still based on clinical diagnosis. To the best of our knowledge, no case of recurrent AFLP in subsequent pregnancies or newborn baby developing fatty acid oxidation defect is reported from our population.

In conclusion, AFLP poses a critical diagnostic and therapeutic challenge. Our case series demonstrated the difficulties in the diagnosis of severe AFLP, which could masquerade as TTP in the setting of pregnancy or overlap with HELLP syndrome. However, the clinical course of patients and some distinctive laboratory tests such as severe hypoglycemia might favor a diagnosis of AFLP. Careful analysis of the clinical progression is important in the recognition of AFLP and prompt termination of the pregnancy is required to improved maternal and perinatal outcomes. In some cases, a definitive diagnosis is difficult, but supportive therapy should be the main target of treatment and must begin as soon as possible.

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